

Children's Work



Year in Review Issue
1984

The Year in Review



The Children's Hospital, founded in 1869, is a voluntary, nonprofit teaching hospital affiliated with Harvard Medical School. The largest pediatric hospital in the country, it is dedicated to patient care, research, and teaching, and offers comprehensive health care services for patients from birth through young adulthood.

Message from the President and the Chairman of the Board

"The Children's Hospital is dedicated to the improvement of the quality of life for children and their families. We seek to provide leadership in the formation and application of new concepts and techniques of child health care and the prevention, diagnosis, and treatment of pediatric disease . . . In the provision of patient care, we are committed to meeting the needs of our patients, their families, and

referring physicians through personalized, responsive, and supportive service. We seek to combine highly caring attitudes and systems with the most advanced technical capabilities to improve the quality of the hospital experience and to obtain the best possible result." (from the Mission Statement for The Children's Hospital)

Underlying Children's three missions of patient care, research, and teaching is the necessity for sound strategic planning. This means identifying future trends in pediatric care and determining our best course of action. The relative swiftness with which change now occurs in health care makes planning particularly challenging.

The President's Office has worked for more than a year with trustees, medical staff, and administrators to forge a strategic plan. The first step in this process was to assess the institution's position relative to the changes occurring in health care and then to identify the key trends that will influence its future role.

Several of these trends are likely to influence the number of patients admitted to pediatric hospitals in the United States and the types of care that will be required.

For example, advances in pediatric medicine are likely to affect our admission levels. As more health problems are cured or controlled, fewer children will require hospitalization. And for those children who are hospitalized, improved treatments for many conditions may continue to shorten the length of stay. This is the kind of trend in pediatric medicine that we at Children's have worked to help bring about through clinical and laboratory research. It is also a trend that must be accounted for in our plans for the future.

A related trend is the marked increase in ambulatory care. For example, many surgical procedures that once required a hospital stay of several days now can be done on an outpatient basis. This benefits patients and their families, while helping to control health care costs. It also reduces significantly the number of patient days for hospitals and the need for certain inpatient services. We must determine the extent to which this trend is likely to continue and how it will affect the use of inpatient and outpatient services.

The changing referral patterns of physicians is another important trend under review. An increasing number of children are obtaining health care through health maintenance organizations (HMOs) and similar groups. Just as we have developed referral relationships with private practitioners in the past, we must develop strong network ties with these groups to ensure ready access to the hospital's services.

Another aspect of this issue is that HMOs, private insurers, and major employers are becoming increasingly concerned about the cost of the health care services they purchase. Some have already begun to contract with hospitals to provide health care services to clients at lower rates. Because Children's is a major teaching hospital offering a highly sophisticated level of care, our rates are often higher than those at community hospitals. This can make Children's less attractive to these health care



David S. Weiner, President



David I. Kosowsky, Sc.D., Chairman of the Board

groups seeking to purchase services more economically. As part of our strategic planning process, we are committed to looking for ways to become more competitive in an increasingly price-sensitive marketplace.

These and other changes will alter both the nature and scope of pediatric health care needs in the years ahead. It is most important that we anticipate the types of services children will need, not just next year, but five years and ten years from now, and into the twenty-first century. With the exceptional academic and clinical leaders on our medical staff, we are in a unique position to carry out such a projection. Over the coming months, this effort will be a top priority for our medical and administrative leadership.

At Children's, we will work to maintain our leadership position in caring for those patients who suffer from illnesses and disorders that require the highly specialized, tertiary care for which Children's is best known. At the same time, we remain committed to providing care for the children who live in our neighborhood and who rely upon us for both hospital and community-based primary care services.

Being responsive to the needs of patients, their families, and others served by the hospital has remained a paramount goal since Children's opened its doors in 1869. Today, patients and their families demand greater participation in their health care. They seek choices and expect the highest standards of care and caring to be met. We

have pledged to redouble our efforts toward providing the best, most responsive services possible for all those who work at and those who use Children's Hospital.

No discussion of the changes that buffet health care today can exclude cost containment and the continued governmental effort to gain control over health care costs. Chapter 372, the state's hospital cost control legislation, has prompted significant changes for hospitals over the past few years. Issues of cost will continue to have a profound effect upon all aspects of health care. Our challenge is to find ways to continue to offer the quality and depth of services that only Children's can provide, while maintaining the strong financial base so vital to the operation of this, the nation's largest pediatric hospital. At the same time, we must continue to advance the pediatric research and teaching programs that are an integral part of the institution and are of such value to improved pediatric care throughout the nation and around the world.

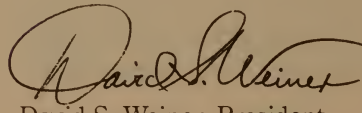
There are other trends we have not mentioned and, no doubt, still more that cannot be anticipated. As we look toward the future, we eagerly await the construction of our new inpatient facility that is scheduled for completion in 1987. This major undertaking has required, and will continue to require, a team effort by the hundreds of individuals associated with Children's. The new facility will be a boon to Children's future. First and foremost, the design of the new building will

enable the hospital to continue to adopt and offer the newest of life-saving procedures. There will be more space to accommodate sophisticated diagnostic and therapeutic equipment. In keeping with our philosophy that parent participation helps speed recovery and ease fears during a child's hospitalization, there will be ample bedside accommodations for parents to be with their child. There will be additional areas for educational activities conducted for hospital staff. And as patient divisions and services move into the new building, much-needed space will become available in the present buildings for support services.

This is a most exciting time for Children's Hospital. In recent months, we have witnessed the introduction of many marvelous accomplishments in organ transplantation,

cardiac surgery, oncology, and other specialties that bring even greater promise and hope for our young patients.

We are confident that with careful, judicious planning by our trustees, medical staff, and administration, Children's will continue on a secure path that will further enhance its well-earned reputation as a world leader. Amid all the changing forces in health care, our most important goals remain: providing state-of-the-art pediatric care, offering a high-quality learning experience for future pediatricians and other health professionals, and conducting research that will result in improved child health.

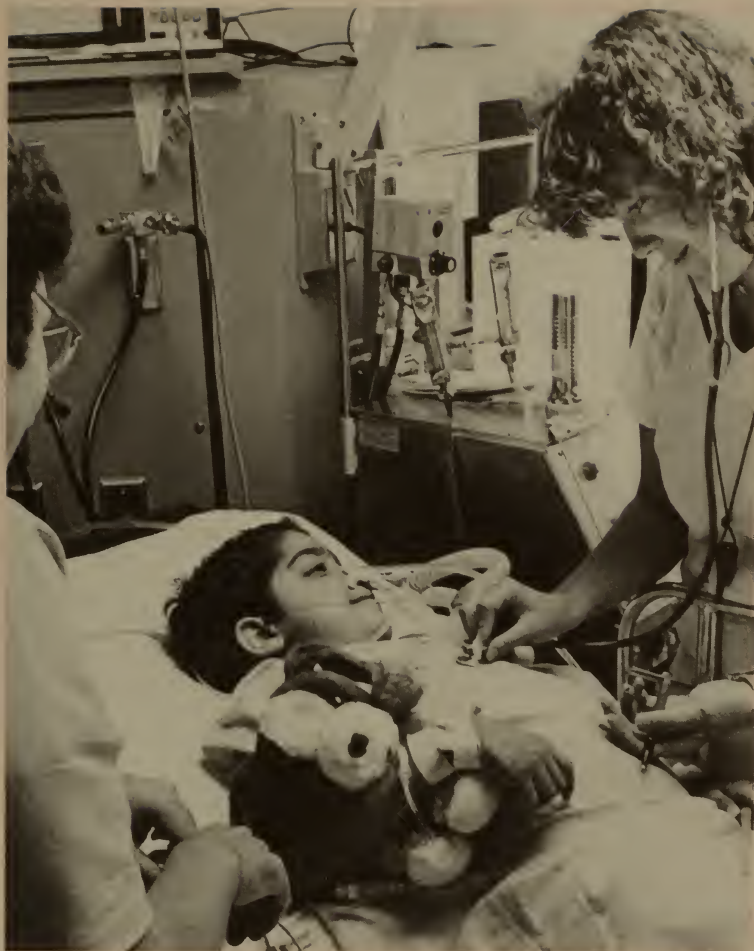
A handwritten signature in cursive script, reading "David S. Weiner".

David S. Weiner, President

A handwritten signature in cursive script, reading "David I. Kosowsky".

David I. Kosowsky, Sc.D.,
Chairman of the Board

1984: Activities and Accomplishments



New inpatient facility. Children's received the long-awaited approval of its Determination of Need (DoN) application from the State Public Health Council in April for the construction of a much needed new inpatient facility. Known as the Blackfan Project, the new 11-story building will be located across from the current main entrance on Blackfan Street. It will feature larger patient rooms to accommodate modern patient care equipment and to allow more parents to stay overnight with their children. There will be larger quarters and more centralized locations for the operating rooms, radiology, and emergency facilities. The current buildings will be renovated to provide expanded space for other support services. Overall, the new facility will help Children's Hospital to better fulfill its missions in patient care, teaching, and research and to keep Children's in the forefront of pediatric health care.

Financing of this major project will be enhanced by the AA (double A) bond rating received by Children's from two major rating agencies, Standard and Poor's, and Moody's.

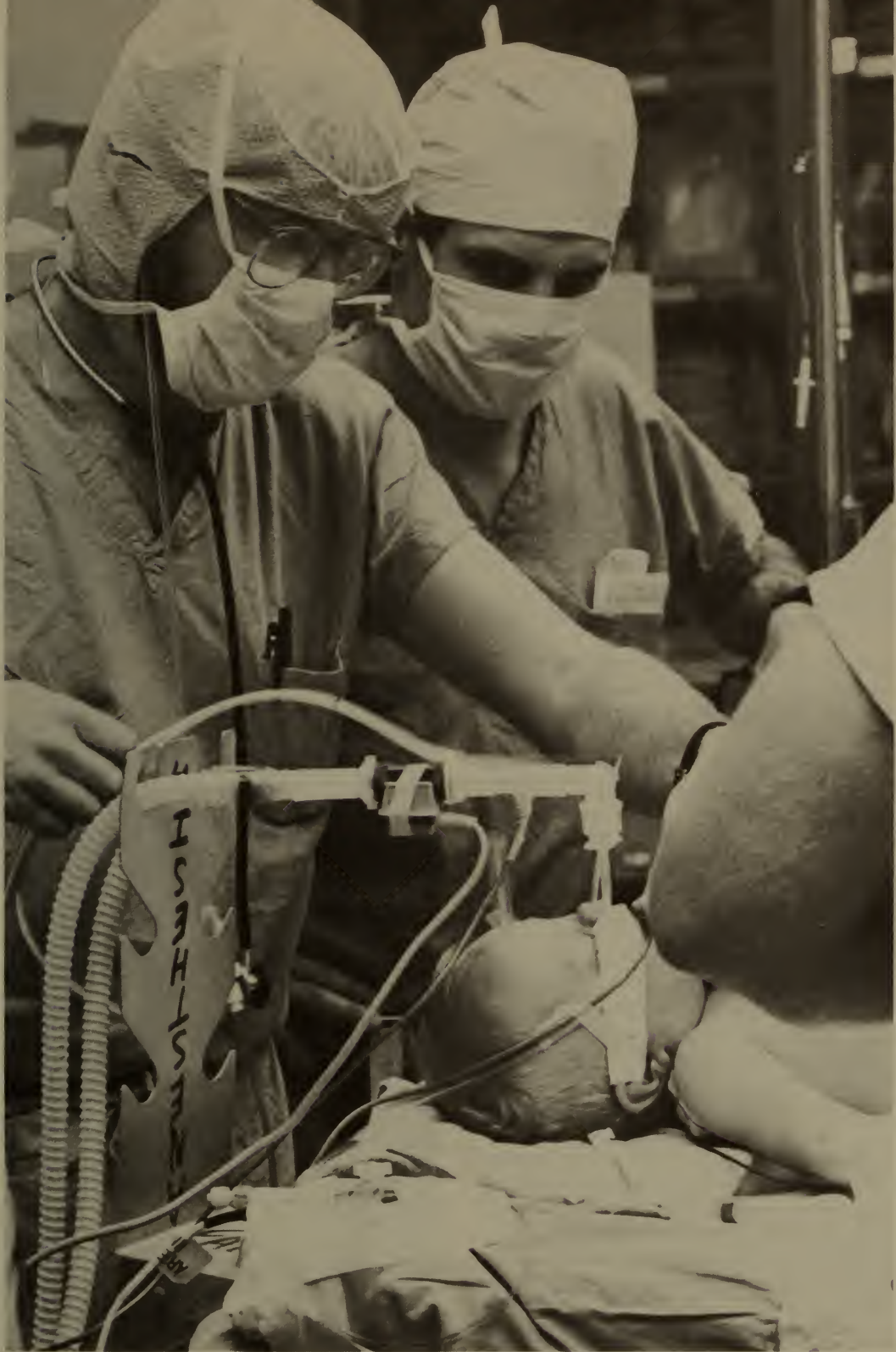
Since the DoN approval, hospital staff, trustees, and architects have worked to refine the building plans in preparation for the groundbreaking scheduled for spring 1985. Completion of the new facility is expected in mid-1987.

First liver transplantation. The first liver transplantation at Children's was performed in April on 15-month-old Joshua Kelley, who was then the youngest liver transplant recipient in New England. Following the 16-hour operation, Joshua remained at Children's for three months and is now a healthy toddler living home with his family in New Hampshire.

The initiation of liver transplantation at Children's resulted from more than a year of cooperative planning by Children's, Massachusetts General Hospital, New England Deaconess Hospital, and New England Medical Center. As members of the Boston Center for Liver Transplantation (BCLT), these four institutions have pooled their resources to share expertise and to reduce the costs of liver transplantation. It is estimated that more than 100 patients in New England could benefit from liver transplants currently. Approximately 40 percent of these are children.

Joshua Kelley, Children's first liver transplantation patient, is 21 months old when with his mother, Bobbie. He passed his routine examination in October with a good report.





A newborn's Hospital roomed its first time these
 pharyngeal muscles etc. After 2 hours time the
 parents 15-month-old Jordan Kelly are the
 patients because a liver transplant in New
 England. Since then, on each mother's protest,
 11-month-old Sebastian Brandis received a liver
 transplant at a child's in Chicago.



ECMO. Physician investigators reported a remarkable breakthrough in the treatment of newborns diagnosed with the most severe type of congenital diaphragmatic hernia. In the past, these infants have not survived for more than one day. Now, with a combination of surgery, anesthesia, and a type of artificial lung, these infants may survive to live a normal life. Diaphragmatic hernia is a condition in which the abdominal organs migrate up into the chest cavity during gestation. This unnatural placement compresses the lungs and greatly impedes the development of air sacs within the lungs.

Soon after birth, surgery is performed on these infants to return the organs to their proper location. However, because the lungs have not fully developed, the infants suffer respiratory distress, and despite intensive intervention in the past, they have died.

Through the new procedure developed at Children's, anesthesia is continued after surgery and an artificial lung, called an extracorporeal membrane oxygenator (ECMO), provides the patient with needed oxygen until the lungs can mature. Although the ECMO was developed in the 60's, its use to save the lives of infants with congenital diaphragmatic hernia is innovative.

Newborn Jim Laumiller was the first patient at Children's Hospital to benefit from an innovative new treatment for diaphragmatic hernia. Joy received in the Massachusetts General Hospital, East Hill, through the care of, left to right, M.D. Dr. Robert C. Allen, M.D. Joseph Yarnall, M.D., assistant in surgery, Dr. O. Thomas, M.D., assistant in anesthesia, and Edward Higgins, R.N.

Overseer/Trustee activities. In December 1983, E. James Morton, president and chief operating officer of the John Hancock Mutual Life Insurance Company, stepped down as a member of the Board of Trustees. Elected to replace him was his colleague, William L. Boyan, executive vice president of corporate operations at John Hancock.

In March 1984, several new overseers attended an orientation program at the hospital to acquaint them with administrative and medical staff members, services, and programs and with the hospital's future plans for growth and development.

The hospital's third Annual Dinner was held at the Museum of Fine Arts in April and was attended by more than 175 trustees, overseers, medical staff members, and guests. Featured speaker for the evening was Mary Ellen Avery, M.D., Children's physician-in-chief, who spoke on the merits of teaching hospitals. Chairman of the Board David I. Kosowsky, Sc.D., announced the recipient of the 1984 Chairman's Award, E. James Morton. Three others involved in hospital activities for many years were

awarded the distinction of Honorary Life Overseer: F. Gorham Brigham, Jr., Mrs. Howard F. Gillette, and George P. Gardner, Jr.

On October 23, 35 overseers and trustees attended a special tour and briefing session to familiarize them with The Children's Campaign, the fund-raising effort to support construction of the new inpatient facility. Guided by members of the Facility Planning Department, overseers saw areas of the hospital that have outgrown their current quarters and that will greatly benefit when relocated in the new, more spacious and functional inpatient facility. They also had the opportunity to ask questions of clinicians in those areas. The program that followed featured a presentation on the new inpatient facility by Director of Facility Planning Rudman Ham and by a project architect from Shepley, Bulfinch, Richardson, and Abbott. Reports were also given by Trustee George Kidder, President David S. Weiner, and Judah Folkman, M.D., director of the Surgical Laboratories.



Physician Dr. Mary Ellen Ham, M.D., is one of the members of the Hospital's Annual Trustees Association.

Research. The largest pediatric research facility in the world is located at Children's. Here research is conducted in virtually every specialty and subspecialty of pediatric medicine.

Heart assist device: The left ventricular assist device (LVAD) currently being tested in the cardiovascular surgery laboratory at Children's is a type of artificial heart. It is a pump that helps circulate blood through the heart's left ventricle in the case of failure of that area of the heart. The left ventricle is the site of more than half of all heart failure. Implanted next to the heart, the device is powered by batteries that are worn in a shoulder halter outside the body. Electric current passes from the battery pack through the skin to the LVAD by means of magnetic induction. This will not cause discomfort for the patient, nor is there an open incision to pose danger of infection.

Unlike the artificial heart pioneered by William DeVries, M.D., the LVAD is not appropriate for patients with failure of both the right and left ventricles of the heart. The LVAD relies upon the heart's right ventricle to function on its own. Physicians hope that this device, once approved for clinical trials by the FDA, will prolong the lives of thousands of patients who now die of heart failure.

Diabetes: As part of a collaborative research project, investigators at Children's have demonstrated that better control of blood sugar in juvenile diabetics can help prevent the development of complications leading to blindness or kidney failure. Inadequate blood sugar control causes thickening of the basement membrane, the outer layer of capillaries, which are the smallest blood vessels connecting arteries with veins. Damage to the basement membrane is believed to be the first stage of devastating complications in the eyes and kidneys.

National study of low birthweight infants: Children's is one of eight institutions to receive a grant in a national collaborative effort to study the health and development of low birthweight infants. Funded by the Robert Wood Johnson Foundation, the four-year study will monitor the effects on these infants of extra support services at the home and through a child development center.

Angiogenesis: This area of research concerns the eradication of tumors by inhibiting the growth of blood vessels that feed them. Recent advances have revealed that by injecting a combination of the drugs cortisone and heparin into animals with a tumor, the growth of blood vessels that feed the tumor is inhibited. When the growth of these blood vessels is inhibited, the tumor loses its source of nourishment and regresses in some, but not all, animals. This important finding presented researchers with another problem to solve; a serious side effect of this treatment was that the high dose of cortisone required suppressed the immune system, thus leaving the host more susceptible to infection. Towards a solution to this, researchers at Children's have found a method to alter the molecular structure of cortisone so that it still inhibits angiogenesis, but does not suppress the immune sys-

tem. Although this research has not reached the stage for clinical trials on humans, the promise of an effective anti-angiogenesis treatment prompts investigators to continue their quest.

Institutional advancements. In the past year, Children's has actively strengthened its support for the Martha Eliot Health Center (MEHC), a neighborhood health service of Children's located in Jamaica Plain.

Major renovations were financed by Children's including expansion of the reception and waiting areas, creation of three new clinical offices and a handicapped-accessible examination room and lavatory, modernization of the laboratory and dental clinic, and rewiring of the electrical system. MEHC handles more than 32,000 patient visits annually.

During 1984, Children's joined with three

The Martha Eliot Health Center, a neighborhood health service of Children's located in Jamaica Plain, received extensive renovations during 1984. (Photo by courtesy of Children's Hospital, Boston, and MEHC.)





*Computer pioneers
Marybeth Briggs
and Pamela Smith
operate the hospital's new
second generation
computer tomography
scanner.*

other hospitals to submit a Determination of Need (DoN) application to the State Public Health Council to form the Boston Center for Heart Transplantation (BCHT). If approved, this organization will enable the member institutions to pool their resources and provide heart transplantation services in a more effective and efficient manner than if each institution provided the service independently. The other BCHT members are Brigham and Women's Hospital, Massachusetts General Hospital, and New England Medical Center.

The Children's Medical Center, the parent corporation of Children's Hospital, has initiated several nonpatient care subsidiaries in addition to The Inn at Children's and Sterling's restaurant. This past spring the corporation opened a fitness center in the apartment building at 400 Brookline Avenue. The fitness center is equipped with circuit weight-lifting apparatus, aerobic conditioning equipment such as a rowing machine and cross-country skiing simulators, and locker room facilities.

Another subsidiary of The Children's Medical Center, Children's Enterprises, Inc., joined a private venture to construct a new medical office building with retail space and a parking garage across from the Enders Building on Longwood Avenue. Called Longwood North, the complex will provide 50,000 square feet of office space, 30,000 square feet of retail space, and public parking for 500 cars. It is scheduled for completion in spring 1985.

Medical staff. Robert Gross, M.D., cardiovascular surgeon-in-chief emeritus, received an honorary degree from Harvard University at commencement exercises in June.

Barry T.S. Smith, M.D., was appointed Director of the Joint Program in Neonatology of Children's, Beth Israel Hospital, and Brigham and Women's Hospital.

The Division of Metabolism was combined with the Division of Endocrinology under the direction of John F. Crigler, Jr., M.D.

The death of Valeria Cavazzuti-Erba, Ph.D., former chief of the Neurophysiopsychological Laboratory in the Department of Neurology's Seizure Unit, was a great loss for her colleagues, as well as family. Among her many significant accomplishments was the development of innovative neurophysiopsychological tests for young patients.

Management changes. Two new administrators joined Children's during the past year: Alexander Ziss was named associate director, and William Hoffman was named associate director for Human Resources.

The hospital's food service management changed hands from an outside firm to in-house management. The department's new name, Nutrition and Food Services, reflects the consolidation of the departments of Nutrition Services and Food Services.

A new smoking policy was instituted, with signs prominently displayed throughout the institution. In an effort to provide healthy surroundings for patients, employees, and visitors, smoking is now permitted only in specifically designated areas.

League continues strong support.

The Children's Hospital League continued its outstanding support for the hospital in 1984. As a result of its many fruitful endeavors, the League donated \$180,000 to Children's. The Festival for Children's Hospital, in its second year, was moved to larger quarters at the Bayside Exposition Center to better accommodate the four-day seasonal celebration. A major feature of the Festival was the sale and display of professionally designed holiday trees and wreaths that were decorated and generously donated by local businesses. The Festival also included entertainment by singers, dancers, clowns, and musicians. For children, a special area called Munchkin Hollow offered creative activities.

While the Festival was launched as a holiday tradition for the League, an old tradition, the League's Yankee Bookstall, took its final bow last spring. A favorite event for bibliophiles, the Bookstall was held for 30 years before the operating costs and the staffing time requirements overtaxed the League's resources.

The League has continued its support of the Summer Garden Activity Program for patients. Hundreds of patients enjoyed activities such as "String art," "Let's be knotty," and "A winter carnival," under the supervision of patient activity therapists in the hospital's Prouty Garden.



The festival in celebration of Children's Hospital's many past seasons was sponsored by the Children's Hospital League. Hundreds of children in various to see the many colorful decorated Christmas trees and to enjoy the festivities.



WBZ Radio announcer Dave Maynard, left, and WBZ-TV news anchor Liz Walker and Jack Williams host the second WBZ-Children's Hospital Fund Telethon in December.

WBZ-Children's Hospital Fund. The WBZ-Children's Hospital Fund, begun by WBZ Radio five years ago to encourage donations for Children's, entered its second year as a cooperative effort between WBZ-TV and WBZ Radio.

Having raised more than 1.5 million dollars for Children's to date, the WBZ-Children's Hospital Fund has grown into one of the most successful events of its kind in the country. Garnering strong community support, the WBZ-Children's Hospital Fund sponsored a variety of fund-raising events during the fall, culminating in December with the WBZ Telethon and three weeks of live broadcasts at Downtown Crossing from the WBZ Radio "Incredible Broadcast Machine." The three-hour telethon told "The Children's Hospital Story" through interviews with patients and their families, staff, and employees. Dozens of Children's staff and volunteers answered telephones at the WBZ studios during the telethon, while many former patients and their families appeared on the broadcast with such personalities as

Dave Maynard, Liz Walker, and Jack Williams. During the telethon, other WBZ personalities were stationed at Quincy Market, the Northshore Shopping Center, the Dedham Mall, and the Natick Mall to collect donations from holiday shoppers for Children's.

In addition to the telethon and Downtown Crossing broadcasts, other events sponsored by WBZ included the Fall Farmstand in September and the Monster Dash Footrace in October.



Children's Hospital employees and short volunteers all volunteer to help during the night of the WBZ Children's Hospital Fund Telethon. Top row, (l) to (r) credit: Richard Rubin, M.D., ophthalmologist-in-chief, Andrea Roversi, Development, Hope Tully, Development, Joan Thompson, executive director, (front row) standing, WBZ weatherman Bruce Selassie, Robert Poirer, M.D., assistant in Anesthesiology, Paul O'Rourke, M.D., assistant in Anesthesiology, Evan Sander, M.D., chief resident Medicine, and Thomas Koscibski, M.D., chief resident Medicine.

WBZ-TV Reporter Charlie Austin and news anchor and public Sarah Wernick were a great team appearing in a public service announcement for the WBZ Telethon to benefit Children's Hospital.



Statistical and Financial Report





Statistics

Patient	1984	1983
Number of licensed beds	339	339
Inpatients served	13,766	13,842
Patient days	101,010	102,813
Average stay	7.3	7.4
Clinic visits	160,605	171,410
Number of clinics	69	70
Emergency room visits	47,600	49,749
Surgical procedures		
Inpatient	7,794	7,907
Outpatient	3,633	3,355
Total	11,427	11,262
Radiology		
Patient visits	64,969	66,766
Procedures performed	71,296	72,877
Laboratory tests	983,592	1,009,040

Personnel	1984	1983
Active medical staff	526	571
Active dental staff	14	14
Associated scientific staff	156	142
Courtesy staff	279	269
House staff	454	439
Consultants	124	145
Emeriti	47	27
Clinical assistants	33	42
Visiting staff	13	15
Nursing staff	755	783
Other full-time employees	1,655	1,481
Other part-time employees	757	807
Volunteers	760	743



Statement of Revenues and Expenses

Years ended September 30,
1984 and 1983

	1984	1983
Patient services revenue	\$135,925,250	\$129,344,746
Contractual adjustments applicable to current year	(16,058,742)	(18,423,669)
Uncompensated services	(6,805,774)	(6,404,527)
Net patient services revenue	113,060,734	104,516,550
Other revenue	10,454,614	9,919,792
Total operating revenue	123,515,348	114,436,342
Patient care expenses	117,597,518	110,386,946
Income from current year patient care operations	5,917,830	4,049,396
Contractual adjustments applicable to prior years	1,813,256	2,573,490
Income attributed to nonpatient care properties . . .	1,798,390	1,588,277
Other	323,362	318,492
Income from operations	9,852,838	8,529,655
Investment income	484,396	466,733
Excess of revenues over expenses	\$ 10,337,234	\$ 8,996,388

Note: The Statement of Revenues and Expenses and Condensed Balance Sheet are excerpted from the audited financial statements and are not intended to provide the information contained in the complete audit report.

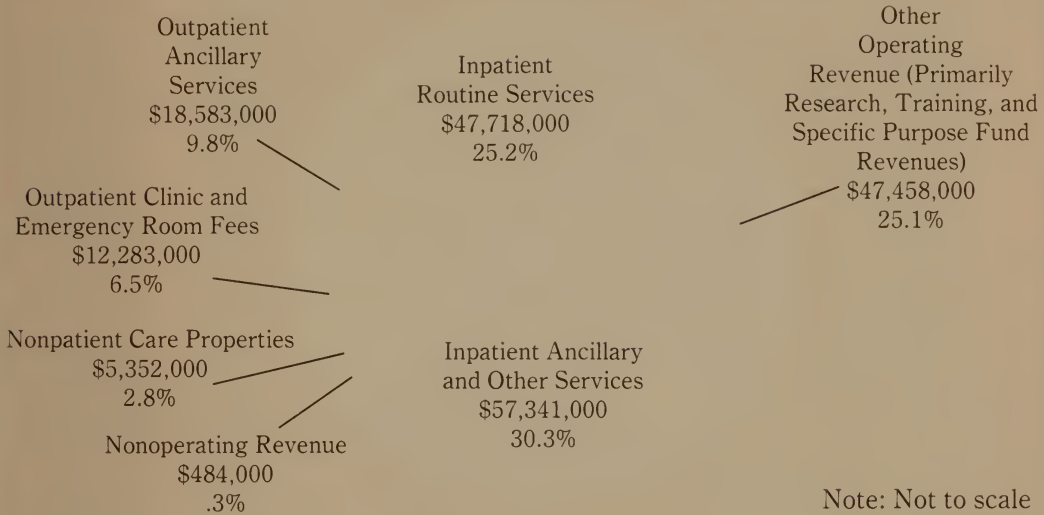
Auditors:

Peat, Marwick, Mitchell & Co.
Certified Public Accountants
One Boston Place
Boston, Massachusetts 02108

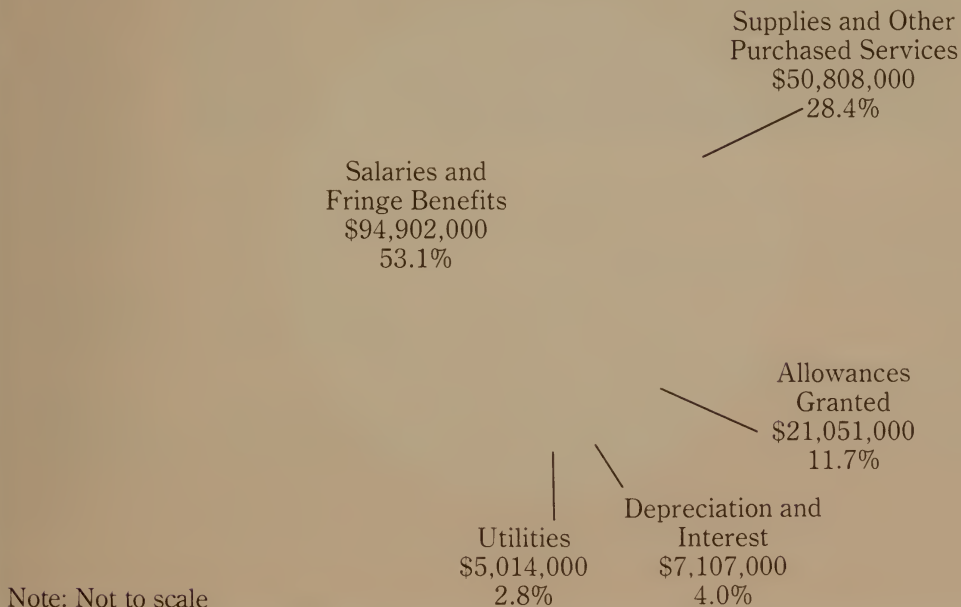


Financial Highlights: Year ended September 30, 1984

Sources of Revenues



Distribution of Expenses





Condensed Balance Sheet: September 30, 1984 and 1983

Assets	1984	1983
Unrestricted funds:		
Current:		
Cash	\$ 1,786,165	\$ 188,558
Investments	2,000,000	2,000,000
Receivables, net	46,124,486	34,279,288
Inventories	1,109,475	955,712
Prepaid expenses	541,772	283,318
Total	<u>51,561,898</u>	<u>37,706,876</u>
Assets held in trust under long-term		
debt agreements	83,258,075	550,000
Plant, property and equipment at cost		
less accumulated depreciation	69,587,115	62,017,043
Other assets	3,965,008	2,775,494
Total	<u>208,372,096</u>	<u>103,049,413</u>
Restricted funds:		
Accounts receivable	3,811,283	3,310,421
Total	<u>\$212,183,379</u>	<u>\$106,359,834</u>

Liabilities and Fund Balances	1984	1983
Unrestricted funds:		
Current:		
Current portion of long-term debt	\$ 75,000	\$ 251,500
Accounts payable and accrued expenses	22,956,438	19,139,492
Due to third-party payors	16,296,614	14,956,819
Total	<u>39,328,052</u>	<u>34,347,811</u>
Long-term debt, excluding current portion	77,040,000	11,669,000
Deferred compensation	2,671,075	2,562,463
Deferred third-party reimbursement	2,793,515	—
Fund balance	86,539,454	54,470,139
Total	<u>208,372,096</u>	<u>103,049,413</u>
Restricted fund balances:		
Specific purpose funds	3,811,283	3,310,421
Total	<u>\$212,183,379</u>	<u>\$106,359,834</u>

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A View of Children's World



I am 13 years old. I was 11 the first time it happened. My mother was out, but the other kids were upstairs. It was evening . . . That first time, he came in and started feeling under my pajamas. I was half asleep and didn't know what was happening . . . I kept telling him no, but he said he'd hurt me if I didn't do it. I told him I didn't want to, but he said yes, I'd like it, and he was just showing me how. I didn't like it. It hurt. He told me not to tell my mother. But then, he did it again and again. I didn't know what to do. He came in maybe once or twice a week . . . I don't know why I let it go on so long. I feel ashamed. I was so scared, and I was afraid someone would find out.

Three years ago, when my son, Kenny, was eight, he joined the hockey team. I was pleased because I thought it would build up his confidence, which he really needed. I was also thrilled because of the reputation of the team's coach. For years I had been hearing how wonderful this man was, how good he was with the kids. He was, simply, the pillar of the community. Since I was a single parent at the time, I was eager to provide Kenny with good male role models. As the season got underway I was really happy for Kenny. The coach really took an interest in Kenny, staying after practice to give him extra help. They started doing more things together—going for

pizza after practice, hiking, movies. One Friday morning Kenny asked if he could stay that night at the coach's house since they would be getting up very early the next day to go hiking. That was the first time that any kind of warning signal went off in my head, but I knew this man was married so I quickly ignored it . . . Six weeks later, Kenny mentioned that he didn't want to go to any more practices that season. He wouldn't say anything more about the subject. The next week my oldest son told me that he had talked to Kenny. He said that for the last two months Kenny was being repeatedly sexually abused by his coach during the times they were alone. Suddenly, I knew he was right.

Sexual Abuse Treatment Team

To members of the Sexual Abuse Treatment Team at Children's Hospital, these stories are familiar ones. Last year, the team offered support and counseling to 178 victims of sexual abuse—children ranging in age from 8 months to 18 years, who had been sexually involved in ways that were inappropriate for their age and level of development. "The definition of sexual abuse includes everything from inappropriate kissing or touching to sexual intercourse," says Frances Sink, Ph.D., co-director of the team at Children's. "But the child's need for support and protection is just as great regardless of the type of abuse."

National estimates point to a dramatic increase in the number of children who are sexually abused each year. According to statistics compiled by the American Humane Association, case reports have increased from 1,975 in 1976 to 22,918 recorded in 1982. These reports are considered to be an underestimation of the magnitude of the problem, as many cases still go unreported.

The interdisciplinary team at Children's was formed six years ago to meet the needs of an increasing number of sexually abused children and their families. Members of the departments of Nursing and Psychiatry

urged that a team be organized that could identify cases of sexual abuse, many of which were not being diagnosed appropriately in the Emergency Room. "When we formed the team, few professionals had any experience in managing sexual abuse cases," explains Renee Brant, M.D., former director and founder of the team. "It was an area in which professionals were reluctant to get involved."

Today the team members offer a wide range of experience. Team members include psychologists, physicians, nurses, social workers, an attorney, and an administrator.

Identifying the problem Though the situations and settings may vary, the cases the team sees share many common aspects. "The abuser is generally very close to the child and is in a caretaking role—either a parent or close relative, even a teacher, coach, or babysitter," Sink says. "This person is usually trusted by the child and often has spent a lot of time building up that trust." She adds, "Contrary to the stereotypical image of the child molester lurking behind school fences, the offending adult is often very upstanding and well-respected—a person you would least suspect of child sexual abuse."

Among the victims of sexual abuse, there is one particularly disturbing similarity: many children feel they cannot tell anyone about it. "The abuse may then go on for a long time, and a child feels increasingly trapped," says Gretchen Graef, M.S.W., co-director of the team with Sink.

This reluctance to tell could have several causes. "Children are taught to obey adults, and if they have been told to keep it a secret, they usually will," Graef explains. "They may also have been threatened to keep it a secret." It was revealed recently that staff members of a California day care center had been abusing children and threatening them to silence by killing small animals to show what could happen to them.

Children also may fear abandonment if they tell. In incest cases, a daughter may feel that her participation in incest is holding her family together and hiding problems that cannot be faced.

Sometimes when a child does tell a parent about an incident, it falls on deaf ears. "This is particularly true of incest cases," Sink says. "A mother can be faced with many conflicting loyalties; if she believes what her child is telling her, then she may have to make a choice to remain with her children or to stay with her male partner." Sink adds that because of these difficult decisions, the mother may choose not to believe the child.

When the abuser is someone outside the family, however, parents are much more likely to believe their child. "Ten years ago that wasn't so," Sink says, "but because of better awareness now, when a child says somebody touched me, people are much more willing to listen and not say it is the child's fantasy."

"Sometimes parents will deny the situation or delay getting help for the child," Brant says. "They will encourage the child to forget about the incident and feel that that's the best way to get over the trauma." But children need to be able to talk about what has happened to them, and to hear that someone cares. "Often forgotten memories about traumatic sexual activities give rise to psychological symptoms and emotional distress later in life," she explains.

How the Team helps "Concerned parents who don't know where to turn often bring an abused child to the Emergency Room," says Kathryn Skidmore, M.S.W., who is head social worker in the Emergency Room and serves as liaison with the Sexual Abuse Treatment Team. More than half of the team's sexual abuse cases are referred through the Emergency Room. An interdisciplinary team, consisting of a physician, social worker, and psychiatrist, is available 24 hours a day to make initial evaluations of sexual abuse cases coming into the Emergency Room. A physician examines the child for evidence of injury or infection, and family members are helped to deal with their immediate concerns and needs. A member of the Sexual Abuse Treatment Team consults with the providers in the Emergency Room and arranges for follow-up by the team within 48 hours. At this meeting, the family's short- and long-term needs are more thoroughly assessed.

"The sexually abused child must be approached with special care," Sink says. A team member asks questions gently about what happened and tries to elicit the child's reactions to the abuse. If children have difficulty telling what has happened to them, they can instead demonstrate by using anatomically correct dolls or puppets to act out the abuse.

A combination of talking and play therapy helps the child to express thoughts and feelings and to better deal with any anxiety, guilt, or confusion. "We will often play with the puppets or the dollhouse in my office, and the child's feelings will really come through," Sink says. "It's not unusual for the child to create a scenario where one puppet repeatedly attacks another puppet, not letting it escape, perhaps killing it, or ordering it into a closet and returning time after time to do bad things to it," she explains. "Some children need to play such a scene over and over again in an effort to master their fears about what has happened to them."

Protection of the sexually abused child is another of the team's most immediate concerns. "One of the most important prognostic factors for the child in terms of how they

will react to the trauma is whether there is someone who will believe, support, and protect them. We need to assess very early on who in the family network will be the child's therapeutic ally," Brant says. She adds, "Unfortunately, a parent or caretaker may not always fill that role."

Siblings may also have trouble dealing with the family disruption and react with denial when a parent is accused, according to Sink. "When this happens, kids are taken out of homes and put in foster homes because they can't find a single ally within the whole family to back them up." She adds, "It's very sad when kids end up losing their families because they get up the courage to tell the truth."

The team recommends steps for protection that make the most sense for the family and situation. They may suggest that the abuser leave, or that the child stay with relatives or in a foster home until adequate protection can be ensured in the home. Richard Bourne, the team's legal consultant, advises on whether to file a "51-A" petition to involve the protective efforts of the Department of Social Services (DSS), which is legally mandated to investigate abuse reports and subsequently protect vulnerable children. DSS must report serious cases, including those of rape or sodomy, to the local District Attorney, who may bring criminal charges.

Family dynamics A team member then meets with the family to try to ascertain what factors may have contributed to the abuse. "The majority of cases reflect family dynamics," Brant says. "Even in nonincest cases, certain family elements may be partly responsible for the child's victimization."

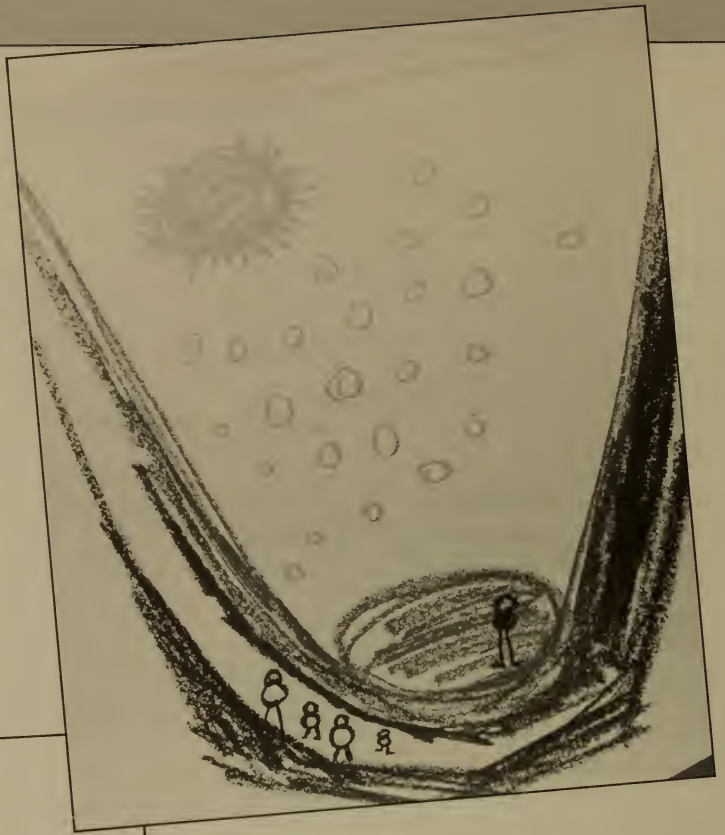
Often parents of sexually abused children were themselves abused when they were young. "We have seen cases where there have been three generations of incest," Sink says. "There are a number of dynamics that may account for this," she adds. A woman who was abused by her father may nonetheless have been attracted to a similar power-abusive man for her choice of spouse, which places her children at similar risk.

Members of the Sexual Abuse Treatment Team include:

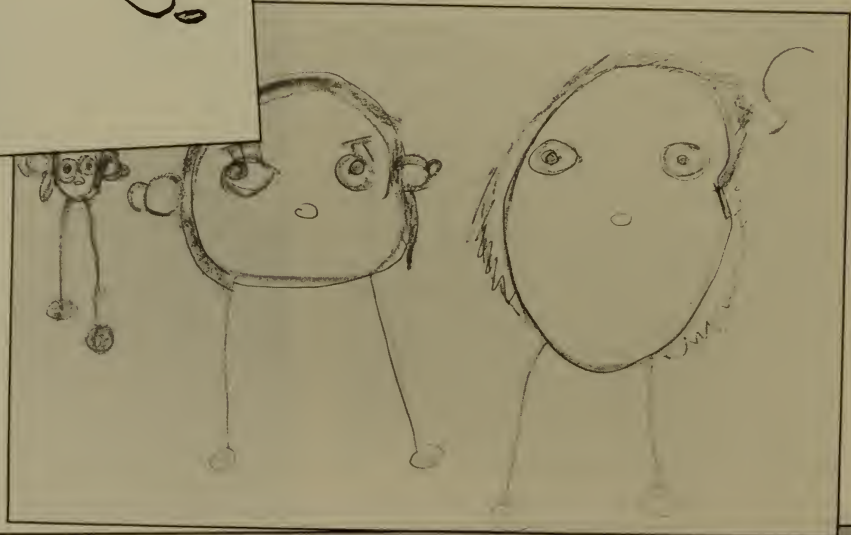
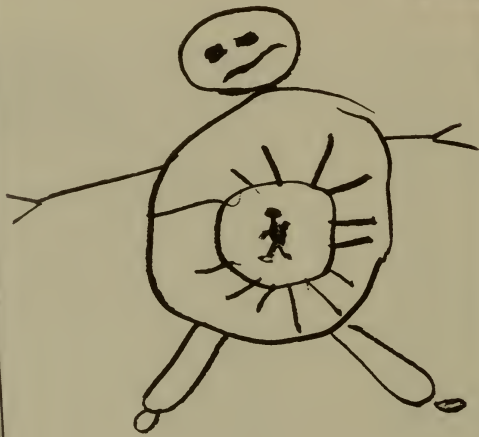
Mary Aruda, R.N., P.N.P., clinical nurse specialist; Donna Baughcum, R.N., psychiatric nurse; Richard Bourne, J.D., attorney; Renee Brant, M.D., psychiatrist; Gretchen Graef, M.S.W., social worker and co-director; Mariette Murphy, M.D., pediatrician; Veronica Serrato, administrative coordinator; Frances Sink, Ph.D., psychologist and co-director; Kathryn Skidmore, M.S.W., social worker and Emergency Room liaison.

Frances Sink, Ph.D., co-director of the Sexual Abuse Treatment Team, uses puppets as a therapy tool to help children out and their families as victims of sexual abuse.





At the end of the tunnel of the giant's foot, children are encouraged to draw pictures to express their feelings. This drawing is a child's drawing of a giant's foot.



Picking up the pieces The emotional impact of sexual abuse depends on the child's age and personality, the relationship of the abuser to the child, and the nature and duration of the abuse. "The child may be confused about what has actually happened and may experience fear, loss of self-esteem, depression, helplessness, or anger," explains Donna Baughcum, R.N., psychiatric nurse. There may be a sense of loss and an adjustment to a changed relationship, if the abuser was close to the child. A longer term effect may be problems with intimacy and developing trusting relationships with others. "In general," Baughcum says, "the closer the relationship and more violent the incident, the more difficult it will be for the child to cope with the experience and the greater will be the need for therapy." The situations vary; a family may need three months of therapy or three years.

The parents' reactions are also an important indicator of how the child will be emotionally affected by the abuse. Parents often feel anger, guilt, or helplessness upon hearing that their child has been sexually abused. Young children may have little understanding of the significance of the incident, so they can be confused if the parents react with intense emotion, and they may incorporate their parents' reactions. "We talk with parents about how they are feeling so they can then help their child to deal with his or her feelings," Skidmore says.

Parents often ask, how could I have let this go on for so long? What could I have done to prevent it? "One of the things that can't be overemphasized is that parents need to be vigilant about warning signals," Sink

says. Parents should be attuned to messages the child may be sending, such as a reluctance to go to a particular place or to be with a particular person, nightmares, new fears, or a need for more reassurance than before. "If a child says, 'I don't want Johnny to babysit,' parents should not think that the child just doesn't want them to go out that night," she explains. "It's important to be aware that sexual abuse is possible, and that it can happen with people that you would least suspect."

The best prevention may be helping children to protect themselves, by letting them know that they can say 'no' if something does not make them feel right, and that it is okay to tell someone they trust.

For the team's five clinicians, managing sexual abuse cases is stressful. But team members support one another. The team meets every Thursday to review cases in progress and to assign new ones, as well as to share the strain. "I've been doing this for three years, and sometimes it is very difficult," Skidmore says. "But I have a lot of support from the other team members." Says Brant, "We feel very rich in having one another. As an interdisciplinary team we can contribute different perspectives to an individual case and improve the outcome for the child and family."

Although the number of sexually abused children continues to rise, the team feels that by understanding and meeting the needs of those victims and their families and by helping to provide an awareness of the issues in the community, they are at least making some progress towards an answer to the problem.

After it happened, I hurt so badly—not physically, just inside of me. But just being able to talk about it really helped. The people at Children's made it easier for me to talk. They listened. I feel so much better about everything now. I feel so much better about myself.*

**comments from a patient treated at Children's Hospital*

Parent Participation

"One source of care and annoyance of officials in children's hospitals comes from the fact that mothers are so often determined to remain with their sick children . . . The mother should never be allowed to remain in the ward and thus demoralize the discipline of the hospital and the other children."

*Ochsner, Albert and Sturm, Meyer, *The Organization, Construction and Management of Hospitals*, Cleveland Press: Chicago, 1907.

Fortunately, those rather oppressive and didactic words were written in 1907, and hospitals have since learned a valuable lesson about the importance of parent participation in a child's hospitalization.

"We find that when parents stay with their child, get involved in their daily care and even in their medical treatments, it has tremendous positive impact on the patient," says Carol Saul, R.N., head nurse on Children's Division 14. "Just being in the hospital—a strange, unfamiliar place—is difficult for a child, but having Mom or Dad there makes it much easier to deal with. In the toddler and pre-school age group, I really believe it helps the child get better faster."

Before the 1940's, most children's hospitals had limited visiting hours and parents were encouraged to "get out of the way" and let professionals take care of the child. However, after World War II, parents and the medical community became concerned about the effects on children of separation from family during hospitalization.

Researchers found that children had a variety of negative reactions to hospitalization including: poor eating or sleeping habits; struggling against treatment and medications; acute fear; withdrawal; regressive, aggressive, or compulsive behavior; and

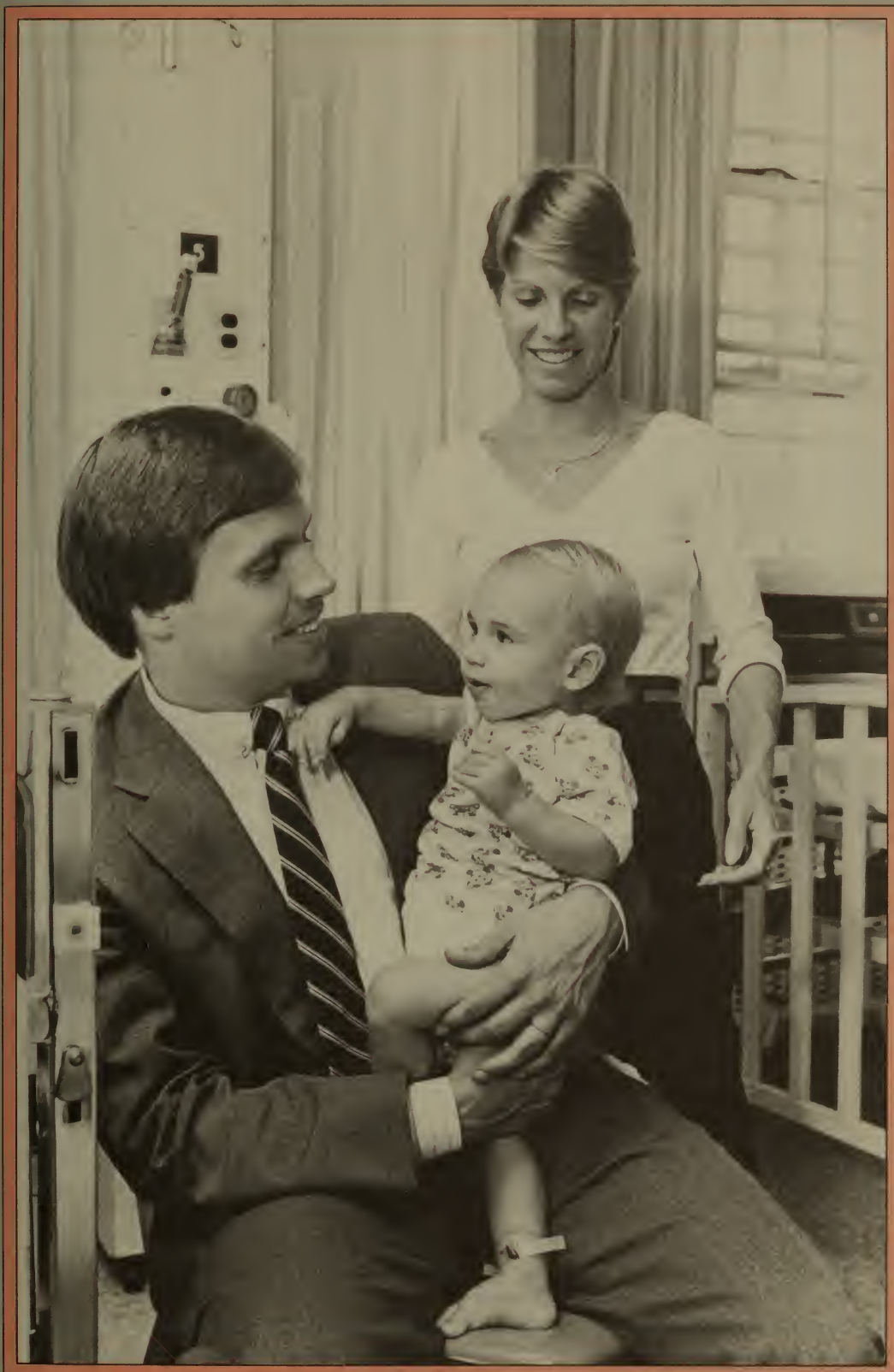
becoming destructive towards their environment or even themselves. It was also discovered that even after patients returned home they often had nightmares, regressed in their behavior, and had difficulties in getting along with others.

Parents know best Today, a child's emotional and psychological well-being is considered as important as his or her physical status. The Children's Hospital has long recognized the many benefits to be gained from parents' involvement with their child's hospitalization.

"Our feeling is that the optimal level of care for any child is achieved through the team work of both parents and nurse," Saul says. "Parents know their child better than anyone else ever will. They know the child's likes and dislikes, how they receive information, what frightens them, and how to comfort them." She adds, "The combination of what the parents know about their child and what the nurses know about the child's medical needs provides the basis for patient care that is much more complete."

More and more studies confirm that the company of a trusted adult does indeed have a positive effect on a hospitalized child. There are reports of lower incidence of emotional problems and infections in children whose mothers remain with them during

Jeff and Linda Marini have taken full advantage of being able to participate in Casey's hospitalization at Children's.



hospitalization, less withdrawal and aggressive behavior, and fewer long-term negative effects.

In addition, studies have shown that these children are often discharged from the hospital earlier than those whose parents are not involved in their medical care. Parents who participate in giving their hospitalized child medications and treatments become knowledgeable and comfortable enough to provide that medical care at home. This is often a significant factor in decreasing the amount of time a child spends in the hospital.

At Children's, visiting hours for parents are 24 hours a day. Parent participation is encouraged on all inpatient divisions. However, not all divisions can provide sleeping accommodations for parents who wish to stay the night. A limited number of cots and fold-out couches are available for this purpose.

Medical and psychological benefits

Susan and Peter Shelsy can attest to both the medical and psychological benefits of

participation in their child's hospitalization. Four-year-old Michael Shelsy was admitted to Children's Division 28 for acute lymphoblastic leukemia. Until the morning he was brought by ambulance to Children's, Michael had not had obvious symptoms. He looked healthy and was able to play normally with his little sister and friends.

"I think it's very important to be here with him," Susan says. "The fact that he didn't feel sick or look sick before he came here and now he's getting daily blood tests, I.V.'s, and medication, is very confusing to him. He needs us here to provide security and answer his questions. He's not a baby, so I know he's going to remember this when he gets older, and I really worry about how the experience is going to affect his psychological development."

Since admission, his mother and father have taken turns staying with Michael. Because Susan and Peter Shelsy live far from the hospital and have a two-year-old daughter at home, each arranged to spend four or five days at a time with Michael. They never left him alone for more than half

Parents help help their son, Michael, mother and father help him, they are not alone. (Susan and Peter Shelsy) Michael is looking to his mother for help and his father for help.



an hour.

In addition to spending the night with their son, both Susan and Peter have become fully involved in Michael's medical care. They are there when his blood is drawn, during bone marrow tests, and for spinal taps. They give him oral medications, fill his I.V. when it empties, and measure his daily weight. "Michael seems to feel better if we're here to hold his hand while he's getting blood drawn or receiving other treatments," Susan says. "I think it's easier for him to have someone here who loves him and whom he knows he can trust while all these painful things are happening to him."

It is also easier on the parents. According to Dorothy Patton, head nurse on Division 28, getting involved in a child's hospitalization is the best way for parents to come to grips with their child's illness. "For many parents, learning about the disease, and sharing in the treatments, medications, and dressing changes, gives them a sense of control over the situation," she says. "They find that the medical aspects of care that they can do become less frightening and it's not a situation where the hospital owns the sick part of the child and the family owns the well part. Hospital people are not going to do anything without the knowledge, consent, and understanding of the parent."

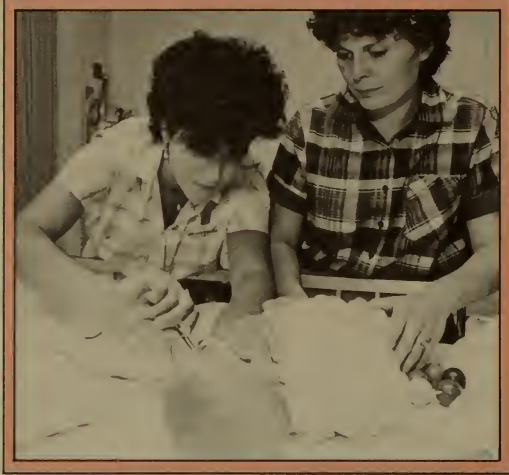
For the first few days after Michael's admission to Children's, Susan was at home with her daughter. "Staying home made it very easy to deny the illness," she says. "It wasn't until I got here and was with Michael for a few days, and could ask three different nurses the same question in a single day, that I could begin to grasp what was really happening. If you're here and involved in the care of your child, you can't help but realize it's something you have to deal with."

Helping parents cope For Linda and Jeff Marini, it began with a call in the middle of the night, a hurried consultation with doctors, and the emergency transfer of their child to a large medical center.

Casey Marini was eight months old when he was first admitted to Children's. "We had taken Casey to our local hospital after he'd become dehydrated from the flu," says his father Jeff. "The next thing we knew, they were telling us they wanted to transfer him to Children's because there was something wrong with his kidney." His mother Linda says, "It was a nightmare. I seriously thought we were going to lose him. I felt they weren't telling us everything."

Susan Shultz holds her son Michael, nursing, while on I.V. on his sickle-cell.





Casey was brought to Children's Emergency Room and tests began immediately. Jeff says, "All I felt was anxiety. The questions kept running through my mind. Is he going to live? Will he be able to have a normal life? Will he need a transplant?"

"It got better that first night when the doctor sat down and explained everything to us," Linda says. "He even diagrammed what seemed to be the problem and answered all our questions. He was very friendly and calm. It made it much easier for us." Keeping parents informed, encouraging them to stay with their child, even during tests and treatments, and answering all their questions as fully as possible is the basis of the family-centered care practiced at Children's.

The Marinis were told that Casey's right kidney had to be removed and that the possibility of additional surgery at a later date could not be ruled out. Linda and Jeff talked with hospital staff. They took out suggested illustrated medical books to read and came back with more questions. Jeff says, "Everyone was very good and understanding and took the time to really explain to us everything we wanted to know."

"One of the most important things for me was being able to be with Casey when he went to the operating room," Jeff says. Linda and Jeff took turns holding Casey while he was sedated in pre-op and until he was relaxed. "You're giving up your child to a stranger and putting a lot of faith in that stranger," Jeff says. "It was much easier to do that after talking with the surgeon and anesthesiologist in depth and actually seeing them when they came to take Casey."

Linda spent almost every night with Casey for the two-and-one-half weeks he

was on Division 14. "It was very important to me to be able to stay overnight, and I think it was very important for him, too. It never even entered my mind that someone would try to separate us, and I would have really protested if I had been told I couldn't stay."

The staff on Division 14 strives to accommodate parents who want to stay with their child, no matter how long the stay. On Division 14, the parents' room has its own refrigerator and coffee pot, individual lockers, and bathrooms and showers for parents' use. Both mother and father are encouraged to stay the night if they wish, although space at a patient's bedside is limited to one parent. Siblings are allowed to visit at any time, and it can be arranged for them to stay overnight.

"We often have a situation where a mother who has a five-year-old on the division is also breastfeeding a newborn," says Saul. "We really want to be able to keep that family unit together."

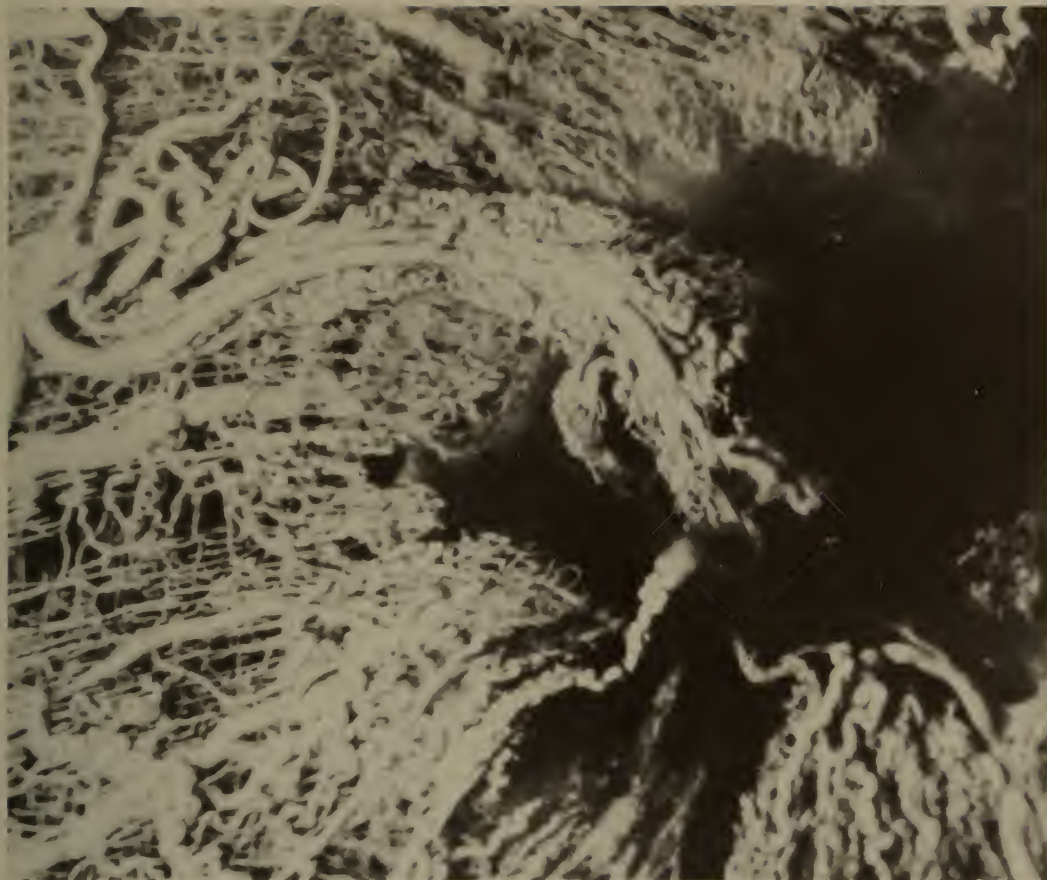
She adds, "The parents are able to form their own little community. They become a great source of support to one another. We've had parents from Roxbury, Wellesley, Bermuda, and Saudi Arabia stay together. All of them are from very different cultural and economic backgrounds, yet they always pull together and become very close."

Linda Marini agrees. "The other parents on the floor always ask you about your child, and they'll refer you to the parents who are veterans for that particular problem. I've made quite a few good friends among the parents that are here."

Jeff's schedule enables him to come in every night by 6 p.m. "That's when most of the fathers come in," he says. "We check up on each other's children and share war stories."

Parents who stay with their hospitalized children—juggling work schedules, private lives, other children—make sacrifices to do so. But they say those sacrifices are nothing compared to how they would feel if they could not be with their children.

Susan Shelsy has experienced both sides. "When I was in nursing school, I did some of my training at a large children's hospital. At the time, we were always told to encourage the parents to take a break. I can remember thinking that some of those mothers were really going overboard because they wouldn't leave their child for even ten minutes. Now, I'm the mother, and I know exactly how they felt."



This photograph shows the proliferation of new blood vessels centering on the site of a tumor. (The tumor has been dissolved.) The new vessels were injected with a latex material designed to better define blood outflow for examination under a microscope. The photograph is magnified 30

times. This experiment was carried out by Loto Henry, M.D., and Robert Ashman, M.D., at the James Graham Brown Cancer Center of the Department of Surgery, University of Louisville, Kentucky. It was made available in the laboratory of Children's in 1997.

Angiogenesis

Like the roots of a tree, the blood vessels form a nutrient-rich network, carrying life-giving blood to the rapidly growing mass of cells. With each beat of the heart, the young cells gain sustenance and strength. As they multiply, the cells form a solid, recognizable mass—one that will affect the life of its host forever.

This growth, however, will be no cause for celebration or euphoric parents, because this is not the creation of life; it is the formation of a potentially deadly cancerous tumor.

In the United States alone, approximately 600,000 new cases of cancer are diagnosed every year—more than 1600 cases every

day. Of those afflicted, more than 8,000 are children.

Thanks to Judah Folkman, M.D., director of the Surgical Research Laboratories at Children's, and his colleagues, a possible new approach for fighting tumors—targeting their blood supply—has emerged. Although it is too early to say how or when this research can be applied to humans, the laboratory findings have led scientists to an increased understanding of how all blood vessels—including those that feed tumors—grow.

Much of the research by Folkman's group during the past two decades has focused on

angiogenesis, the growth of new capillary blood vessels, also called neovascularization, and how it relates to the growth of normal and cancerous body cells.

"Angiogenesis activity can be expressed in normal, as well as malignant cells," Folkman explains. "In some cases, the growth of new blood vessels can be life-saving, since these vessels are a vital part of the healing process."

In people who have heart attacks, for example, angiogenesis is one way the body can grow new blood vessels to route around clogged arteries to reach oxygen-starved muscle. And in wounds, new capillaries form to aid the healing process.

"The major difference between angiogenesis in normal tissue and angiogenesis in malignant tumors," Folkman says, "is that blood vessel growth is self-limited in normal tissue. That is, it shuts off when the blood vessels have completed their function." However, the angiogenesis that occurs during tumor formation continues unchecked, bringing the tumor a constant flow of nutrients that will support cell growth until the tumor has been eradicated or until the host dies.

In 1960, Folkman and his colleague, Frederick Becker, M.D., began to study this process at the Naval Medical Research Institute in Bethesda, Maryland. Their experiments suggested that the growth of blood vessels was a vital step in the development of a tumor. But, they still did not know how the tumor cells initiated blood vessel growth.

After a series of experiments in the mid-60's, Folkman says, he began to realize that the absence of blood vessel growth might actually limit the growth of solid tumors. Folkman's hypothesis, that blood vessel formation could actually control tumor growth, was considered unorthodox. "This hypothesis was met with a great deal of skepticism," Folkman recalls, "since most researchers had always believed that angiogenesis was a side effect, rather than a control point, of tumor growth."

With the genesis of Folkman's hypothesis, however, an entirely new research approach to studying tumor formation evolved, one that attempted to control the vascularization process before the tumor had a chance to grow and spread. But, researchers still needed to find how tumors stimulated this vessel growth. To do so, they continued their in-depth study of the process of tumor formation.

Tumor formation Experiments with rabbits that Folkman carried out in the early 1970's with Michael Gimbrone, M.D., and Ramzi Cotran, M.D., who are now associate professor and chairman of Pathology at Brigham and Women's Hospital respectively, suggested that most solid tumors begin as a collection of multiplying cells. These cells live on nutrients in the surrounding body fluids until they reach the size of a tiny pea. This phase of tumor growth, before the tumor connects to the host's vascular system, is called the avascular phase. At this stage of its development, the tumor lacks its own network of blood vessels for supplying nutrients, including oxygen, and for removing wastes.

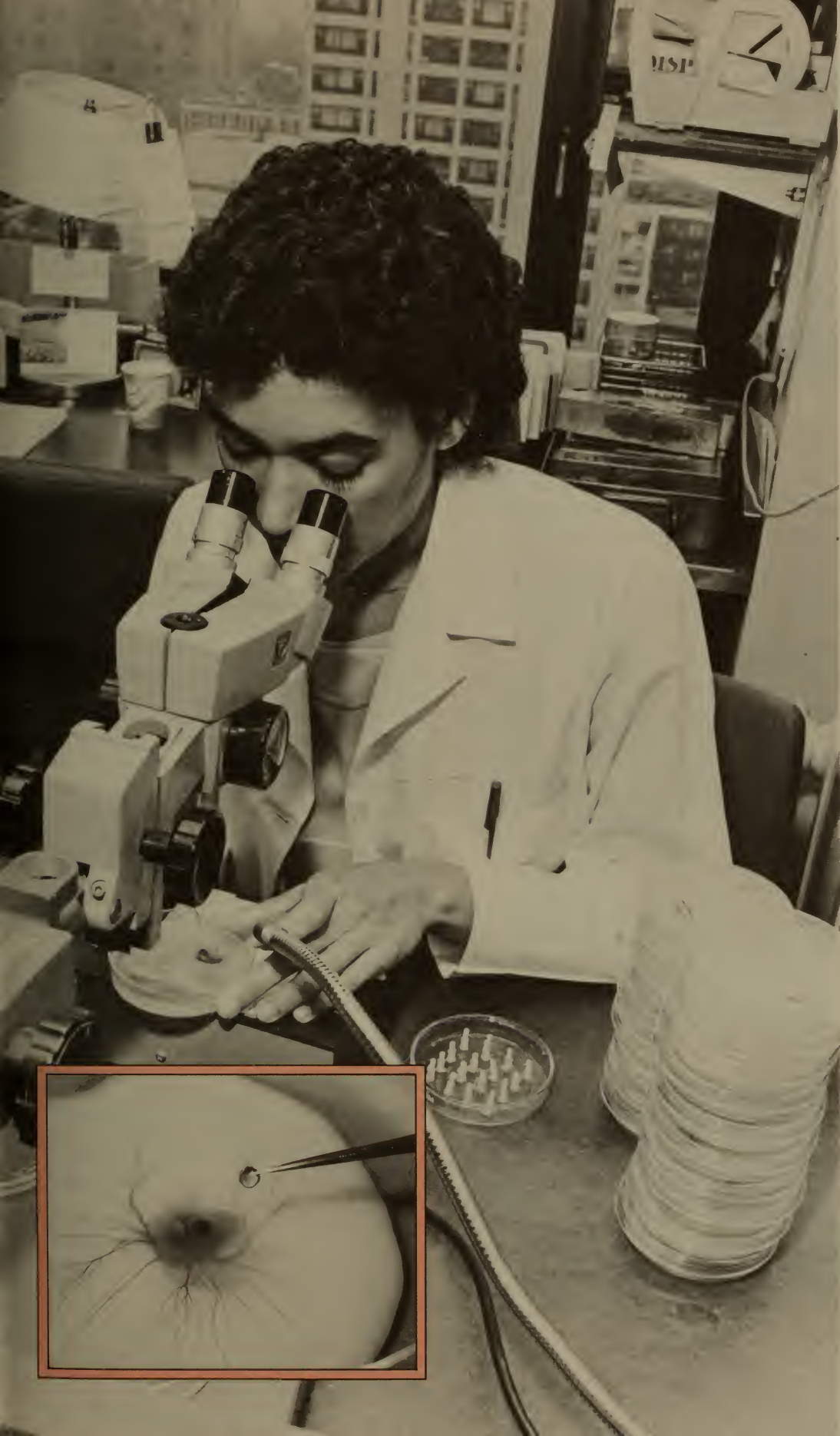
In the second phase, called the vascular phase, the tumor appears to stimulate the growth of thousands of new capillary blood vessels, each thinner than a hair. Once these vessels reach the tumor, Folkman says, "it may enlarge as much as 16,000 times its original volume in only two weeks." The vascularized, enlarging tumor can be seen by X-ray or may be felt. It can invade nearby tissue and can send cells to other parts of the body, a process known as metastasis.

Most solid tumors are now thought to evolve through these two distinct phases, avascular and vascular. "One of our research team's objectives was to try to determine how the tumor stimulated the growth of these new blood vessels," Folkman says.

To that end, Folkman and his fellow researchers launched their search for the biological signal that attracts new vessels to a tumor. By 1971, they were able to report the isolation of a substance from tumors that could stimulate the outgrowth of new vessels. However, the specific agent, or tumor angiogenesis factor (TAF), was in a very crude, impure form, mixed with many other proteins.

Tumor angiogenesis factor (TAF) The effort to obtain a completely pure angiogenic factor from a tumor continued through the next 12 years and was at times discouraging and frustrating, Folkman recalls.

Rosa Ciren, fourth-year student at Harvard Medical School, places a methylcellulose disc on a 3-day-old chick embryo. The disc contains a test substance to be analyzed for angiogenesis activity. Each disc is up of methylcellulose disc being placed in chick embryo.





Developing vessels carrying blood from tumor to its capillary network. The picture is showing a micrograph of angiogenic factors.

New techniques had to be developed and required the contributions of the entire Surgical Laboratories team and of colleagues from associated institutions.

For example, capillary endothelial cells, the cells from which the smallest vessels in the body are made, had never been grown outside the body in a laboratory. This was finally achieved after five years of work, with the help of Bruce Zetter, Ph.D., now research associate in Surgery at Children's, and Christian Haudenschild, M.D., now professor of Pathology at Boston University's Mallory Institute. These endothelial cells could then be used to detect the presence of angiogenic factors.

The separate stages of capillary growth had to be figured out in order to understand at what point the factor had its effect, an effort led by Dianna Ausprunk, Ph.D., currently research associate in Surgery at Children's.

New polymers had to be developed that could be implanted in animals to slowly release the TAF factor, day after day, similar to how a tumor would release it. Robert

Langer, Ph.D., now research associate in Surgery at Children's, guided this effort, and many Massachusetts Institute of Technology students came to the Children's Surgical Laboratories to work on different aspects of the problem.

As the angiogenic factor was being purified, it had to be tested in the presence of living blood vessels. For this purpose, Folkman's group used chicken eggs. The chick embryo experiments were greatly improved by two medical students, John Barlow and Stephanie Taylor, now pediatric resident and intern, respectively, at Children's. Finally, in the past year, Yuen Shing, Ph.D.; Michael Klagsbrun, Ph.D.; and Joanne Murray, Ph.D., all research associates in Surgery at Children's, were able to report the purification of a tumor-derived factor that stimulated growth of the capillary cells in a medium contained in dishes and stimulated blood vessel growth in the eggs.

Angiogenesis inhibitors discovered

During the long effort to purify an angiogenic factor, the researchers also searched for substances that could inhibit angiogenesis directly. One of these turned out to be protamine. This drug is used in the hospital to neutralize the anticoagulant or blood thinning action of heparin, a substance secreted by a type of connective tissue cell known as a mast cell. Taylor found that protamine also canceled the ability of heparin to enhance angiogenesis. In fact, protamine by itself could reduce tumor angiogenesis and slow tumor growth considerably. Unfortunately, protamine had toxic side effects at the level that was necessary to inhibit tumor growth. The researchers continued to hunt for other angiogenesis inhibitors.

An unexpected finding The subsequent finding of the most potent angiogenesis inhibitor to date caught the researchers by



A five-year-old child is treated with heparin and a heparin-like substance as an angiogenesis inhibitor to slow tumor growth. Angiogenesis research could lead to new treatments for such children with the development of a safe source of heparin to cause regression in the growth of these angiogenic blood vessels.

surprise. Taylor and Folkman were trying to increase the sensitivity of the chick embryo for testing angiogenic activity. One problem with this assay is that when a window is made in the egg shell, dust from the shell often causes inflammation, making tumor angiogenesis more difficult to view. They decided to add cortisone, a steroid hormone that is commonly used to suppress inflammation.

"The results were totally unexpected," Folkman says. "Heparin plus cortisone inhibited angiogenesis. The combination was a potent inhibitor of the growing vessels in the chick embryo, caused regression of large tumor masses, and inhibited metastases in some, but not all, animals tested."

The high dose of cortisone that was necessary, however, suppressed the immune system, thus making the animals more susceptible to infection. This side effect would limit the use of combinations of heparin and cortisone in patients. However, Rosa Crum, a Harvard medical student, and Folkman have recently found that the structure of cortisone can be altered so that only its anti-angiogenic activity remains. These altered compounds do not have cortisone's negative side effects.

Possible clinical applications In the future, if angiogenesis inhibitors can be made safe enough and effective for human use, a number of new therapies may be possible. In thinking of the clinical applications, researchers in the Surgical Laboratories are asking these questions. Could children disfigured by hemangiomas, a congenital form of tumor, which consists principally of excessive blood vessels, be helped by inducing regression of the hemangioma in its earliest stage? Would it be possible to stop the abnormal growth of new blood vessels in the

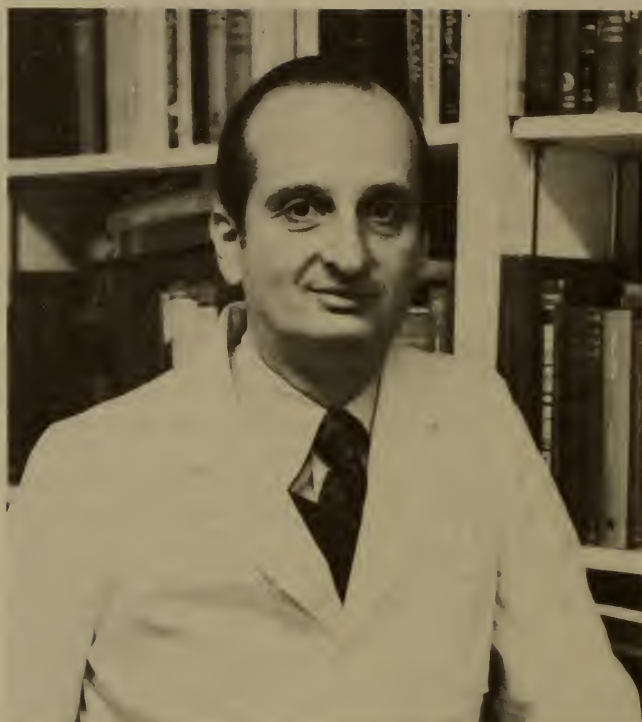
eyes of premature infants, or of adults with diabetes? To what extent might an angiogenesis inhibitor reduce the excessive growth of capillaries in the skin of patients with psoriasis, or in the joints of patients with arthritis? Will angiogenesis inhibitors be useful in cancer chemotherapy or as an adjunct to X-ray therapy?

Those afflicted by these and other diseases in which angiogenesis contributes to the progression of the disease may some day benefit from the remarkable research efforts of Folkman and his colleagues. But, many questions need to be answered and more research needs to be done before clinical trials can be undertaken.

"We still don't know if normal body processes will be affected by inhibitors of vascularization," Folkman says. If so, the researchers need to know the effect these inhibitors will have on regulating normal cell processes, such as wound healing or embryonic development.

Ten years ago, the terms "angiogenesis inhibitor" and "angiogenesis stimulator" were not to be found in the medical literature. Now they are used commonly by scientists in university laboratories and pharmaceutical companies in many parts of the world. The persistence and dedication of the researchers at Children's continues, as does the hope that the refinement of antiangiogenesis therapy will provide effective treatment for patients suffering from diseases affected by angiogenesis.

Dr. Folkman's laboratory is supported by grants from the National Cancer Institute, the American Cancer Society, The Franzheim synergy Trust, and by a grant to Harvard University from the Monsanto Company.



Judah Folkman, M.D., is director of the Surgical Research Laboratories at Children's Hospital and Julia Dyckman Andrus Professor of Pediatric Surgery, and Professor of Anatomy, at Harvard Medical School. Folkman was Surgeon-in-Chief at Children's for 14 years before stepping down in 1981 to resume his research activities full time.

Under Folkman's direction, the Department of Surgery pioneered many programs, including hyperalimentation (feeding by vein), craniofacial reconstruction, and establishment of a kidney dialysis and transplantation program. In addition, Folkman's own research has built a solid scientific foundation for the field of tumor angiogenesis.

Earlier in his career, Folkman discovered

that drugs could be released slowly through implants of silicone rubber, which became the basis for modern sustained-release technology. He was also involved in the development of the first implantable synchronous pacemaker, the forerunner of the modern pacemaker. With Robert Gross, M.D., cardiovascular surgeon-in-chief emeritus, Folkman assisted the laboratory team in the development of heart-lung pumps and designed a method for the repair of ventricular septal defects.

Folkman received his M.D. degree magna cum laude from Harvard Medical School in 1957. He trained in general surgery at Massachusetts General Hospital and in pediatric surgery at Children's Hospital of Philadelphia.

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